

PERSISTENT HEARTBURN, BARRETT'S OESOPHAGUS AND OESOPHAGEAL CANCER



Action Against Heartburn – Before it's too late

Charities promoting earlier diagnosis of oesophageal cancer.

A joint awareness campaign supported by:

Association of Upper GI Surgeons (AUGIS)
Barrett's Oesophagus UK (formerly Barrett's Oesophagus Campaign)
Barrett's Wessex
British Society of Gastroenterology (BSG)
Campaign Against Reflux Disease (CARD)
Cancer Research UK
Fighting Oesophageal Reflux Together (FORT)
Gastro Oesophageal Support and Help (GOSH) Bristol
GUTS UK (formerly CORE)
Gutsy Group
Heartburn Cancer UK (HCUK)
Humberside Oesophageal Support Group (HOSG)
Michael Blake Foundation
OCHRE (Scotland)
Oesophagoose – Oesophageal and Gastric Cancer Awareness Campaign
OG Cancer NI (Northern Ireland)
Oxfordshire Oesophageal and Stomach Organisation (OOSO)
Primary Care Society for Gastroenterology (PCSG)
UK Barrett's Oesophagus Registry (UKBOR)

www.actionagaintheartburn.org.uk

Medical Advisor: Dr Jason Dunn.

PERSISTENT HEARTBURN, BARRETT'S OESOPHAGUS AND OESOPHAGEAL CANCER

The size of the problem of oesophageal cancer

Oesophageal (or gullet) cancer is the seventh most common cause of cancer death in the United Kingdom (2016). Each year in the UK around 9,000 people are diagnosed with oesophageal cancer, and over 7,000 die from it¹². Only 15% of adult oesophageal cancer patients in England and Wales survive their cancer for five years or more.³ Oesophageal cancer mortality rates increased in the UK between the 1970s and early 2000s, though in the past decade mortality rates have fallen in the UK, in line with the trend in many other developed countries.⁴ For males, European age-standardised (AS) mortality rates increased by 72% between 1971-1973 and 2003-2005 and then decreased by 7% between 2003-2005 and 2012-2014. For females, rates increased by 35% between 1971-1973 and 1995-1997 and then decreased by 17% between 1995-1997 and 2012-2014.⁵

It has been estimated that 950 UK lives could be saved each year if the rate of early diagnosis and outcomes of oesophago-gastric cancer matched the best in Europe.⁶

One prediction concludes that as the population ages, there will be 12,657 cases of oesophageal cancer in the UK in 2035.⁷

The UK has the joint-highest incidence of oesophageal cancer in Europe for men and the highest for women.⁸ Across the UK, incidence rates are highest in Scotland and lowest in Northern Ireland.⁹ Within England there is a north-south divide, with incidence rates highest in the North West.¹⁰ In 2007, the Chief Medical Officer drew attention to a rise, over the previous two decades, in the incidence of oesophageal cancer (87% for men).¹¹

Early diagnosis makes a crucial difference to outcomes. Nationally, around a fifth of cases are only diagnosed in patients admitted to hospital as an emergency, with a corresponding tendency for them to be too late for curative treatment.¹² Diagnosis at an early stage by endoscopy is particularly important, as it has been shown to improve treatment outcomes compared to late stage cancers.

Types of oesophageal cancer

There are two main types of oesophageal cancer: squamous cell carcinoma (OSCC) and adenocarcinoma (OAC). OSCC (around a quarter (28%) of oesophageal cancers in the UK) tends to occur in the upper two thirds of the oesophagus and is associated with smoking and alcohol consumption. The age-standardised rate of OSCC is rising in England alone¹³.

OAC (about 70%¹⁴) occurs mainly at the lower end of the oesophagus near the junction with the stomach, is not generally related to alcohol consumption but is associated with a pre-cancerous condition called Barrett's Oesophagus (BO), persistent acid reflux and obesity.^{15 16 17} OAC tends to occur in younger patients than OSCC, and its incidence is rising rapidly. The UK is reported as having the

highest incidence of OAC in the world.¹⁸ The average annual age-standardised incidence rates for oesophageal adenocarcinoma in England alone has increased by around 18.7% from 7.3 per 100,000 people between 2003-2005 to 8.6 per 100,000 between 2011-2013¹⁹.

Gender differences

Around 7 in 10 oesophageal cancer cases in the UK are in men²⁰. For adenocarcinoma (see below) in England the male:female ratio is even higher at 4:1.²¹

Age Profile

More than 95% of oesophageal cancer cases are diagnosed in patients aged 50 years or more. Almost nine in ten cases in the UK are in people aged 60 and over, and incidence increases with age. The profile plateaus in the eighth decade.

Barrett's Oesophagus (BO), the only known precursor lesion for oesophageal adenocarcinoma, occurs earlier; 18% of those diagnosed with BO are under 50 years of age.²² The age profile for BO diagnosis is becoming progressively younger, and there are some reported cases progressing to adenocarcinoma in their 30s and 40s.

Why Acid Reflux is Important

Gastro-oesophageal reflux (GOR) is associated with OAC, which represents 70% of the cases of oesophageal cancer in the UK. It occurs when stomach contents (mainly acid but also bile) rise up into the oesophagus due to impaired function of the valve (lower oesophageal sphincter – LOS) between the oesophagus and the stomach. This may lead to a burning sensation known as heartburn, since the normal lining of the oesophagus is not designed to withstand acid and bile.

Gastro-oesophageal reflux disease (GORD) is a very common condition, with 30-40% of the UK population experiencing regular heartburn²³. In 2010, the number of prescriptions for heartburn / dyspepsia totalled 58 million at a cost of £336 million.²⁴ There were approximately 50m prescriptions for PPI (proton pump inhibitor) medication (eg Omeprazole, Esomeprazole, Lansoprazole, Losec) to reduce stomach acid in 2013-14²⁵. These figures exclude the additional thousands of over-the-counter purchases.²⁶

Heartburn is sometimes combined in medical records with dyspepsia as an indigestion issue.

Smoking and alcohol can relax the LOS and thereby contribute to GORD. Chocolate might have a similar effect. A hiatus hernia can also be relevant because the LOS comes to lie above the diaphragm where it is unable to function properly. Obesity, and indeed some postural issues such as sitting on very low chairs after a meal, can lead to upward pressure that pushes stomach acid into the oesophagus. Stress can also increase GORD, as can a diet high in fatty food that takes longer to digest.

There is a high rate of reflux and obesity in the UK compared with Sweden, which may explain the UK's rate of OAC being five times higher than that of Sweden.²⁷ Most people who suffer from acid reflux, for a variety of reasons, will not develop complications, but there are estimated to be between 375,000 and one million people in the UK who have Barrett's Oesophagus, that carries a cancer risk.²⁸

It is estimated that around 10% of *persistent* heartburn sufferers will develop BO, and that 10% of those with BO will eventually develop cancer.

Barrett's Oesophagus as a cancer risk factor

Barrett's Oesophagus (BO, also called *Columnar Lined Oesophagus*) is thought to be an acquired condition, though the cause remains unclear. An association between reflux of stomach acid (which is necessary for digestion and should normally be prevented from rising into the oesophagus by the LOS) and BO has been demonstrated by a landmark study.²⁹

It is thought that prolonged exposure to stomach acid and bile can lead to the cells lining the oesophagus being replaced by columns of cells that are similar to those of the stomach or intestine. These columnar cells are thought to protect people against the pain of heartburn as the cells can withstand acid: this may explain the phenomena of the heartburn stopping after a number of years; and of patients presenting with BO who report only mild or no heartburn. As a result of not being adequately treated, the BO continues to be assaulted by refluxate, and the cells may start to develop in a disorderly pattern called *dysplasia*, a condition that increases the risk of adenocarcinoma.

A sustained period of acid reflux in the past is therefore also a risk factor, notwithstanding that symptoms can resolve with PPI medication.

It is prudent for doctors to review and properly examine patients who have taken PPI medication for a significant period to clarify the diagnosis of the underlying condition. This may often involve an endoscopy. It is important to investigate for potential BO because of the risk of adenocarcinoma.

The British Society of Gastroenterology (BSG) Guidelines on the Management of Barrett's Oesophagus recommend endoscopic screening be considered in patients with chronic GORD symptoms and multiple risk factors (at least three of: aged 50 years or older; white race; male gender; obesity) but that the threshold of risk factors should be lowered in the presence of family history including at least one first degree relative with BO or OAC.³⁰

National Institute of Clinical Excellence (NICE) Guidelines on Dyspepsia and GORD provide for patients with persistent, unexplained dyspepsia or reflux symptoms to have a discussion with their GP about referral to a specialist service.³¹

The changed cells in the Barrett's Oesophagus columns may resemble those of the stomach or intestine. If the latter, this is referred to as intestinal metaplasia (IM). In the USA, absence of a finding of IM has led to cases not being defined as Barrett's; in the UK it has been shown that IM is not as relevant as was once thought since the

malignant risk is similar whether IM is present or not. DNA abnormalities (which may be present with or without IM) are better predictors of malignant risk than IM³². Recent research in America has suggested significant genetic links.³³ There is evidence that Barrett's patients with a rhesus negative blood group are at a higher risk of progression to cancer.³⁴ BO cases can cluster in families.

The length of the BO segments can be significant, with a higher risk of cancer in Barrett's segments over 7cms in length³⁵.

The risk of Barrett's Oesophagus progressing to oesophageal adenocarcinoma is reported in the medical literature as being between 0.3% and 0.6% per year^{36 37 38 39} which translates to an overall lifetime risk of 7.5-12.5%, depending on several factors. The lifetime risk may be as high as 25%, but the situation is complicated, especially from a patient's point of view, by the fact that it is rare to know when Barrett's Oesophagus first *starts to develop*, as distinct from when it is first *diagnosed*. Risk of progression has been shown to be higher in male patients, concurrent smokers, patients with a family history of oesophageal cancer and long segment length. A specialist investigation and biopsies, followed by surveillance, are therefore important in this situation. The presence of low grade or high grade dysplasia multiplies this risk, and are indicators for intervention with endoscopic eradication therapy at a specialist centre.

It must also be noted that 90% of patients with non-dysplastic BO will have a constant cell type that will not progress to cancer, and are more likely to die from an unrelated disease.⁴⁰

Dysplasia is at present the most robust routinely used clinical marker of cancer progression in Barrett's oesophagus. Currently, these cell changes can only be assessed after endoscopy with biopsy, where small pieces of tissue are removed and then looked at under the microscope. Histology (microscopy) reports may refer to 'gastric type mucosa' or 'glandular epithelium of the gastric type' rather than the more accurate 'columnar-lined oesophagus'.

Barrett's Oesophagus is present in the majority of all OAC cases but will not be seen if the tumour has arisen from a non-Barrett's source or if a large tumour has overgrown the original Barrett's⁴¹. The mortality rate for all oesophageal cancer in a group of patients already known to have Barrett's Oesophagus was found to be 11-fold higher than would otherwise be expected in a comparable group without Barrett's, and in relation to OAC it was 25 times higher.⁴²

Surveillance Endoscopy

Patients diagnosed with BO are checked at intervals by surveillance endoscopy, in order to identify dysplasia and treat it with endoscopic therapy when the disease is potentially curable. BSG guidelines recommend surveillance every 2-5 years depending on the length of Barrett's segment. The use of high-resolution endoscopy is recommended, to be carried out in a structured way for standardised measurement of the Barrett's segment (the Prague classification). Biopsies are recommended of nodular lesions if present, and random biopsies every 2cm from four quadrants. Advanced imaging modalities, such as chromoendoscopy or 'virtual

chromoendoscopy' (i.e Narrow Band Imaging (Olympus), I-scan (Pentax) or FICE (Fuji)) are not recommended for routine use but may have a role for patients at higher risk of progression. The finding of dysplasia in BO needs a confirmatory repeat endoscopy with appropriate treatment at a specialist oesophageal cancer centre.

Treatment

Barrett's oesophagus with high risk features can now be treated in many cases by either destroying or removing the affected cells by endoscopy, without the need for surgery⁴³. In the UK, endoscopic therapy is now the standard care for Barrett's oesophagus demonstrating high grade dysplasia (HGD) and early cancer. Recently the BSG and NICE have approved these techniques for the treatment of persistent or confirmed Low grade dysplasia. Techniques include Endoscopic Mucosal Resection (EMR), Radiofrequency Ablation (RFA) and, for small 'islands', Argon Plasma Coagulation (APC). Photodynamic Therapy (PDT) has been superseded by RFA and is seldom used now. These techniques should be performed at centres where endoscopic and surgical options can be offered to patients. All patients with dysplasia or early cancer, for whom therapy is considered, should be discussed at the specialist Multi-Disciplinary Team meeting for oesophago-gastric cancer. The 2014 National Oesophago-Gastric Cancer Audit reflected the recent trend towards endoscopic therapy, finding that 39.6% of treatments for HGD were EMR, 14.4% were RFA and 5.6% were surgery. Surveillance was offered as a management option in 35% of HGD cases despite the apparently high cancer risk.

The ASPECT trial was reported in 2018 as showing that taking Esomeperazole and aspirin can reduce the risk of developing cancer for those with BO.⁴⁴

Other symptoms of oesophageal cancer

Late symptoms of oesophageal cancer are difficulty or pain in swallowing food, food sticking in the gullet, and unexplained weight loss. In the presence of these symptoms, the cancer has often progressed to a stage when the opportunities for curative treatment are greatly reduced.

Better diagnosis of Barrett's Oesophagus is an opportunity for making an impact on earlier diagnosis of oesophageal adenocarcinoma that is not available for many other types of cancer.

'Action Against Heartburn' - The Awareness Campaign's messages

The key messages of this awareness campaign are:

- Consult your GP if you have
 - persistent heartburn, particularly at night, for three weeks or more.
 - persistent indigestion, for three weeks or more.
 - persistent hiccups or regurgitation of food
 - difficulty or pain in swallowing food
 - unexplained weight loss.

- Do not keep taking over-the-counter digestion remedies week after week without seeing your GP to investigate underlying causes (which most frequently will be less serious than cancer)
- GPs should consider a review of patients taking prescription remedies for reducing stomach acid after an appropriate period.
- An endoscopic examination is the only sure way of detecting Barrett's oesophagus or oesophageal cancer. This may need to include those at a younger age than the current profile for diagnosis.
- Diet, obesity, stress, tobacco and alcohol may contribute to heartburn. There are good reasons for us to address these issues, even if they do not contribute to us developing cancer.

¹ Annual average number of oesophagus cancer (ICD10 C15) cases in **the UK** between **2013 and 2015**.

² Annual average number of oesophagus cancer (ICD10 C15) deaths in **the UK** between **2014 and 2016**.

³ Cancer Research UK (<http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer#heading-Four>)

⁴ http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx?cancer=oesophagus

⁵ Cancer Research UK <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/mortality#heading-Two>

⁶ Abdel-Rahman M, Stockton D, Racht B, Hakulinen T, Coleman MP. *What if cancer survival in Britain were the same as in Europe: how many deaths are avoidable?* Br J Cancer 2009;101:Suppl 2:S115-24.

⁷ <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/incidence#heading-Six>

⁸ http://globocan.iarc.fr/Pages/summary_table_site_sel.aspx

⁹ <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/incidence#heading-Zero>

¹⁰

<https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland>

¹¹ *A Pathological Concern – Understanding the Rise in Oesophageal Cancer*. CMO Annual Report 2007

¹² Routes to Diagnosis 2006-2015 workbook (a), http://www.ncin.org.uk/publications/routes_to_diagnosis.

¹³ Cancer Research UK. The annual average squamous cell carcinoma incidence rates (defined specifically as ICD-O3 M805-M808, considering behaviour code 3 only) are based on cases diagnosed in England between 2003 and 2013. Please note that the recording quality of this data is quite low and there are difficulties in defining the exact morphology each cancer site, meaning that there are likely to be further cases that have not been classified with the appropriate morphology coding within this dataset.

¹⁴ Victoria Coupland of Thames Cancer Registry quotes 58.5% OAC for England for 2008 with 12% unknown morphology, and 64.2% lower oesophageal cancer (8.5% not known). Cancer Research UK give the proportion of OADC as just over half (from Devita et al, *Cancer - Principles & Practice of Oncology 8th edition 2008*, p.1000; PMID:19513070).

<http://cancerhelp.cancerresearchuk.org/type/oesophageal-cancer/about/types-of-oesophageal-cancer#adeno>

¹⁵ Lagergren J, Lagergren P. *Oesophageal Cancer – Clinical Review*. BMJ. 2010; 341.

- ¹⁶ Lagergren J, Bergstrom R, Lindgren A, Nyren O. *Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma*. *New Eng J Med* 1999;340:825-31.
- ¹⁷ O'Doherty MG, Freedman ND, Hollenbeck AR, Schatzkin A, Abnet CC. *A prospective cohort study of obesity and risk of oesophageal and gastric adenocarcinoma in the NIH–AARP Diet and Health Study*. *Gut* 2011;10:1136
- ¹⁸ Arnold M, Soerjomataram I, Ferlay J, & Forman D *Global Incidence of Oesophageal Cancer by Histological Subtype in 2012* *Gut* doi:10.1136/gutjnl-2014-308124
- ¹⁹ Cancer Research UK. The annual average adenocarcinoma incidence rates (defined specifically as ICD-O3 M814-M838, considering behaviour code 3 only) are based on cases diagnosed in England between 2003 and 2013. Please note that the recording quality of this data is quite low and there are difficulties in defining the exact morphology each cancer site, meaning that there are likely to be further cases that have not been classified with the appropriate morphology coding within this dataset.
- ²⁰ <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/incidence#heading-Zero>
- ²¹ *Incidence of Oesophageal Cancer in England* National Cancer Intelligence Network (NCIN) Data Briefing. (www.ncin.org.uk/publications/data_briefings/incidence_of_oesophageal_cancer_in_england)
- ²² Wall CM, Charlett A, Caygill CP, Gatenby PA, Ramus JR, Winslet MC, et al. *Are newly diagnosed columnar-lined oesophagus patients getting younger?* *Eur J Gastroenterol Hepatol* 2009,21:1127–1131.
- ²³ El-Serag HB & Talley NJ *Systemic review: the prevalence and clinical course of functional dyspepsia* *Aliment Pharmacol Ther*. 2004 Mar 15;19(6):643-54.
- ²⁴ *NHS PCT Board Prescribing report. Drugs for dyspepsia-prescribing guidelines and discussion points.2010*
- ²⁵ *Be Clear on Cancer* Stakeholder presentation 3 December 2014
- ²⁶ Reckitt Benckiser reflux advice at www.rb.com/home
- ²⁷ Löfdahl HE, Lane A, Lu Y, Lagergren P, Harvey RF, Blazeby JM, et al. *Increased population prevalence of reflux and obesity in the United Kingdom compared with Sweden: a potential explanation for the difference in incidence of esophageal adenocarcinoma*. *Eur J Gastroenterol Hepatol*. 2011;23:128-32.
- ²⁸ Caygill CP, Reed PI, Hill MJ, Watson A. *An initial comparison of nine centres registering patients with the UK National Barrett's Oesophagus Registry (UKBOR)*. *Eur J Cancer Prev* 1999; 8:539-542.
- ²⁹ Lagergren J, Bergstrom R, Lindgren A, Nyren O. *Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma*. *New Eng J Med* 1999;340:825-31
- ³⁰ Fitzgerald R, Di Pietro M, Ragnath K, Ang Y et al *British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus*. *Gut* 2014 Jan;63(1):7-42 <http://www.bsg.org.uk/clinical-guidelines/oesophageal/guidelines-on-the-diagnosis-and-management-of-barrett-s-oesophagus.html>
- ³¹ NICE quality standard Dyspepsia & GORD CG184. List of quality statements (QS96): Statement 5. 'Adults with persistent, unexplained dyspepsia or reflux symptoms have a discussion with their GP about referral to a specialist service'.
- ³² Reid B et al. *Predictors of Progression to Cancer in Barrett's Esophagus: Baseline Histology and Flow Cytometry Identify Low- and High-Risk Patient Subsets* *American Journal of Gastroenterology*, Vol 95, No 97, 2000. Dunn JM et al *Comparison of nuclear texture analysis and image cytometric DNA analysis for the assessment of dysplasia in Barrett's oesophagus* *British Journal of Cancer* (2011) 105, 1218–1223. doi:10.1038/bjc.2011.353. Bird-Lieberman EL et al. *Population-based study reveals new risk-stratification biomarker panel for Barrett's esophagus* *Gastroenterology*. 2012 Oct;143(4):927-35.e3. doi: 10.1053
- ³³ Orloff M, Peterson C, Xin H, Ganapathi S, Heald B, Yang Y, et al. *Germline Mutations in MSR1, ASCC1, and CTHRC1 in Patients With Barrett Esophagus and Esophageal Adenocarcinoma* *JAMA*. 2011; 305(22):2353-2353
- ³⁴ Caygill CP, Royston C, Charlett A, Wall CM, et al. *Barrett's blood groups and progression to oesophageal cancer: is nitrous oxide the link?* *Eur J Gastroenterol Hepatol*. 2011 Sep;23(9):801-6.

-
- ³⁵ Anaparthi R, Gaddam S, Kanakadandi V *et al.* *Association Between Length of Barrett's Esophagus and Risk of High-grade Dysplasia or Adenocarcinoma in Patients Without Dysplasia.* *Clin Gastroenterol Hepatol* 2013.
- ³⁶ Shivaram Bhat, Helen G Coleman, Fouad Yousef, Brian T Johnston *et al.* *Risk of Malignant Progression in Barrett's Esophagus Patients: Results from a Large Population-Based Study.* *JNCI J Natl Cancer Inst* (2011) doi: 10.1093/jnci/djr245.
- ³⁷ Nicholas J Shaheen & Joel E Richter. *Barrett's Oesophagus* *Lancet* 2009; 373:850-61
- ³⁸ Piers A. Gatenby, Christine P. Caygill, Christine Wall, Santanu Bhattacharjee *et al.* *Lifetime Risk of Esophageal Cancer and Endoscopic Surveillance Burden in UK Patients With Barrett's Esophagus.* *Gastroenterology* Vol. 140, Issue 5, Supplement 1, Pages S-222-S-223
- ³⁹ Spechler SJ *Barrett's Esophagus and Risk of Esophageal Cancer: A Clinical Review* *JAMA* 2013;310(6):627-636
- ⁴⁰ Desai TK, Krishnan K, Samala N, Singh J *et al.* *The Incidence of Oesophageal Adenocarcinoma in non-dysplastic Barrett's Oesophagus: a meta-analysis.* *Gut.* 2012 Jul;61(7):970-6
- ⁴¹ As reported by Dr Jane Darnton, retired Clinical Research Scientist with a special interest in microscopy and oesophageal disease.
- ⁴² Caygill CPJ, , Royston C, Charlett A, Wall CM, Gatenby PAC *et al.* *Mortality in patients with columnar-lined oesophagus (CLO)* *Gastroenterology* 2010; 138: S-16
- ⁴³ Spechler SJ, Sharma P, Souza RF, Inadomi JL, *et al* *American Gastroenterological Association Medical Position Statement on the Management of Barrett's Esophagus.* *Gastroenterology* 2011;140:1084–1091
- ⁴⁴ <http://www.cancerresearchuk.org/about-us/cancer-news/press-release/2018-06-04-taking-aspirin-and-anti-acid-reflux-medication-prevents-oesophageal-cancer-in-high-risk-patients>